IN THE SPECIFICATION:

Please replace the paragraph beginning at page 7, line 22, with the following rewritten paragraph:

E1 The present invention is further directed to the murine homologue of human VEGF (referred to herein as "mVRF"). The mVRF has approximately 85% identity and 92% conservation of amino acid residues over the entire coding region compared to human VEGF. The mVRF is encoded by a nucleic acid molecule comprising a nucleotide sequence substantially as set forth in Figures 9A-9D.

Please replace the paragraph beginning at page 9, line 16, with the following rewritten paragraph:

E2 Figures 1A-1D show the nucleotide sequence (SEQ ID NO:1)and corresponding amino acid sequence (SEQ ID NO:2) of $VEGF_{165}$.

Please replace the paragraph beginning at page 9, line 19, with the following rewritten paragraph:

E3 Figures 2A-2F show the nucleotide sequence (SEQ ID NO:3) and corresponding amino acid sequence (SEQ ID NO:4) of SOM175.

Please replace the paragraph beginning at page 9, line 22, with the following rewritten paragraph:

E4 Figures 3A-3B show the results of BLAST search with SOM175 protein sequence.

Please replace the paragraph beginning at page 9, line 24, with the following rewritten

paragraph:

E5 Figures 4A-4D show the BESTFIT alignment of VEGF cDNA and SOM175 cDNA.

Please replace the paragraph beginning at page 9, line 26, with the following rewritten paragraph:

E6 Figures 5A-5F show the multiple alignment of $VEGF_{165}$ with SOM175 and its splice variants at the nucleotide level.

Please replace the paragraph beginning at page 9, line 29, with the following rewritten paragraph:

E7 Figures 6A-6C show the multiple alignment of $VEGF_{165}$ with SOM175 and its splice variants at the amino acid level.

Please replace the paragraph beginning at page 10, line 7, with the following rewritten paragraph:

E8 Figures 9A-9D show the nucleotide and predicted peptide sequences derived from mVRF cDNA clones. Numbering of nucleotides are given on the left, starting with the A of the initiation codon. Amino acids are numbered on the right, starting from the first residue of the predicted mature protein after the putative signal peptide has been removed. The alternatively spliced region is double underlined and the resulting peptide sequence from each mRNA is included. A potential polyadenylation signal is indicated in boldface. Start

E8 Cont.

and stop codons of $mVRF_{167}$ and $mVRF_{186}$ are underlined and a polymorphic AC repeat in the 3' UTR is indicated by a stippled box. The positions of intron/exons boundaries are indicated by arrowheads.-

Please replace the paragraph beginning at page 10, line 17, with the following rewritten paragraph:

--Figures 10A-10B show the BESTFIT alignments of human and murine VRF protein isoforms. A: $mVRF_{167}$ and $hVRF_{167}$. B: $mVRF_{186}$ and $hVRF_{186}$ from the point where the sequences diverge form the respective 167 amino acid isoforms. Amino acid identities are marked with vertical bars and conserved amino acids with colons. An arrow marks the predicted signal peptide cleavage site of human and mouse VRF.-

E9

Please replace the paragraph beginning at page 10, line 23, with the following rewritten paragraph:

--Figures 11A-11B show the BESTFIT alignment of $mVRF_{167}$ and $mVEGF_{188}$ (Brier et al., 1992) peptide sequences. An arrow marks the signal peptide cleavage site of mVEGF. Identical amino acids are indicated by vertical bars and conservative substitutions by colons. Numbering of amino acids is as described in the legend to Figure 9.-

E10

Please replace the paragraph beginning at page 11, line 8, with the following rewritten paragraph:

--Figures 14A-14E show film autoradiographs (A-C) and dark-field micrographs (D-E) illustrating the expression pattern of mVRF and mRNA in the mouse. In the E14 mouse embryo (A) positive signals are present over the developing heart (Ha) and

E11

cerebral cortex (Cx). A low background signal is also present over other tissues in the section. In the E17 embryo (B) and the heart (Ha) is clearly visible due to a strong hybridisation signal. An equally strong signal is present over brown adipose tissue (Fa) in the back and around the thoracic cage. A moderate hybridisation signal is present over the spinal cord (SC) and the tongue (T). The background signal is reduced compared with the E14 embryo. In the young adult mouse (C-D), positive signals are present over the heart (Ha) and adipose tissue (Fa) around the thoracic cage, while, for example, the lungs (Lu) are unlabeled. The hybridisation signal over the heart is evenly distributed over the entire left ventricle, including papillary muscles (D). In the E17 heart hybridised with an excess of cold probe, no positive signal is present (E). Scale bars = 0.5 mm (A), 1.2 mm (B), 1 mm (C), 0.3 mm (D), 0.1 mm (E).

E11 Cont

Please replace the paragraph beginning at page 11, line 23, with the following rewritten paragraph:

-- Figures 15A-15D show dark – (A and C) and bright-field (B and D) micrographs showing mVRF mRNA expression in mouse adipose tissue (A-B) and spinal cord (C-D). A strong hybridisation signal is present over fat (A), as shown by the strong labeling in Sudan black stained sections (B). A weak signal is present also in skeletal muscle (M in A-B). In the adult spinal cord (C) the mVRF probes gave a neuronal staining pattern over the gray matter. Toloudine counterstaining showing that motoneurons in the ventral horn (D), interneurons in the deep part of the dorsal horn and around the central canal (not shown)

E12

E12 Cont

where largely positive for mVRF mRNA. Scale bars = 0.1mm (A), 0.1 mm (B), 0.25 mm (C), 0.015 mm (D).

Please replace the paragraph beginning at page 12, line 1, with the following rewritten paragraph:

Figures 16A-16C show the effect of VEGF on embryonic day 8 (E8) chick

E13

sensory neurons as determined by % survival (Fig. 16A), % neurite outgrowth (Fig. 16B) and average neurite length (μm) (Fig. 16C).

Please replace the paragraph beginning at page 12, line 4, with the following rewritten paragraph:

Figures 17A-17C show the effects of VEGF and SOM175 on chick glia.

E14

Tested were CNS glial (Fig. 17A), peripheral glia (Fig. 17B) and CNS oligodendrocytes (Fig. 17C).

Please replace the paragraph beginning at page 15, line 18, with the following rewritten paragraph:

The entire sequence of the cDNA clone (SOM175) was compiled and is shown in Figures 2A-2F with its corresponding amino acid sequence. This sequence was

E15

screened for open reading frames using the MAP program (GCG, University of Wisconsin). A single open reading frame of 672bp was observed (see Figures 2A-2F). There appears to be little 5' untranslated sequences (2bp). The 3' untranslated region appears to be complete as it includes a poly-adenylation signal poly-A tail.

Please replace the paragraph beginning at page 15, line 25, with the following rewritten paragraph:

--Database homology searches were performed using the BLAST algorithm (run at NCBI, USA). This analysis revealed homology to several mammalian forms of VEGF (see Figures 3A-3B). The amount of homology between SOM175 and human $VEGF_{165}$ was determined using the BESTFIT program (GCG, University of Wisconsin; see Figures 4A-4D and 5A-5F). Nucleotide homology was estimated at 69.7% and protein homology was estimated as at least 33.3% identity and 52.5% conservation using BESTFIT analysis. BLAST analysis on nucleotide sequences revealed the almost complete match to a human expressed sequence tag EST06302 (Adams et al., 1993).--

E16

Please replace the paragraph beginning at page 16, line 1, with the following rewritten paragraph:

--These data indicate that SOM175 encodes a growth factor that has structural similarities to VEGF. Both genes show start and stop codons in similar positions and share discrete blocks of homology. All 8 cysteines as well as a number of other VEGF residues believed to be involved in dimerisation are conserved. These residues are Cysteine-47, Proline-70, Cysteine-72, Valine-74, Arginine-77, Cysteine-78, Glycine-80, Cysteine-81, Cysteine-82, Cysteine-89, Proline-91, Cysteine-122 and Cysteine-124 and are shown in Figures 6A-6C. Given the structural conservation between VEGF and the SOM175 gene product it is also possible that they share functional similarities. It is proposed that SOM175 encodes a VEGF-like molecule that shares some properties with VEGF but has unique

E17

E17 cnt properties of its own. The nucleotide sequence and corresponding amino acid sequence of $VEGF_{165}$ is shown in Figures 1A-1D.

Please replace the paragraph beginning at page 16, line 14, with the following rewritten paragraph:

E18 --The percentage similarity and divergence between $VEGF_{165}$ family and SOM175 family (protein) were analysed using the Clustal method, MegAlign Software, DNASTAR, Wisconsin. The results are shown in Tables 2.1 and 2.2. The alternatively spliced forms of SOM175 are abbreviated to SOM715-e6 where all of exon 6 is deleted; SOM715-e6 and 7 where all of exons 6 and 7 are deleted; and SOM175-e4 where all of exon 4 is deleted. The spliced form of SOM175 are shown in Figure 7. Genomic maps of SOM175 showing intron/exon boundaries are shown in Figures 8A and 8B.-

Please replace the paragraph beginning at page 24, line 23, with the following rewritten paragraph:

E19 --Murine VRF homologues were isolated by screening a murine cDNA library with an hVRF cDNA clone. Five clones of sizes varying from 0.8-1.5 kb were recovered and sequenced. The cDNA sequences were compiled to give a full length 1041 bp cDNA sequence covering the entire open reading frame (621 bp or 564 bp depending on the splice form, see below) and 3' UTR (379 bp), as well as 163 bp of the 5' UTR (Figures 9A-9D).-

Please replace the paragraph beginning at Page 25, line 3, with the following rewritten paragraph:

The predicted N-terminal signal peptide of hVRF appears to be present in mVRF with 81% identity (17/21 amino acids). Peptide cleavage with mVRF is expected to occur after reside 21 (Figures 10A-10B). These data suggest that mature mVRF is secreted and could therefore conceivably function as a growth factor.

E-20

Please replace the paragraph beginning at Page 25, line 8, with the following rewritten paragraph:

As with hVRF, two open reading frames (ORFs) were detected in cDNAs isolated by library screening. Four of five clones were found to be alternatively spliced and lacked a 101 bp fragment homologous to exon 6 of hVRF. The predicted peptide sequences of the two isoforms of mVRF were determined and aligned with the corresponding human isoforms (Figures 10A-10B).

E-21

Please replace the paragraph beginning at Page 25, line 14, with the following rewritten paragraph:

The message encoding $mVRF_{186}$ contains a 621 bp ORF with coding sequences terminating at position +622, towards the end of exon 7 (Figures 9A-9D). The smaller message encoding $mVRF_{167}$ actually terminates downstream of the +622 TAG site due to a frame shift resulting from splicing out of the 101 bp exon 6 and the introduction of a stop codon (TGA) at position +666, near the beginning of exon 8 (Figures 9A-9D).

E-22

Please replace the paragraph beginning at Page 25, line 21, with the following rewritten paragraph:

The $mVRF_{186}$ protein has strong homology to the amino and central portions of VEGF while the carboxyl end is completely divergent and is alanine rich. $mVRF_{167}$ possesses these similarities and also maintains homology to mVEGF right through to the C-terminus (Figures 11A-11B). The overall homology of $mVRF_{167}$ to $hVRF_{167}$ was 85% identity and 92% similarity, respectively (Figures 10A-10B). Likewise, homology between $mVRF_{167}$ and mVEGF (Breier, et al. 1992) was 49% identity and 71% conservative amino acid substitution, respective (Figures 11A-11B).

E-23

Please replace the paragraph beginning at Page 25, line 29, with the following rewritten paragraph:

A canonical vertebrate polyadenylation signal (AATAAA) (Birnstiel, et al., 1986) was not present in the mVRF cDNA, however, the closely matching sequence GATAAA is present at similar positions in both mouse and human VRF cDNAs (Figures 9A-9D). In contrast to hVRF, mVRF was found to contain an AC dinucleotide repeat at the extreme 3' end of the 3'UTR (nucleotide positions 998 to 1011, Figures 9A-9D). Polymorphism of this repeat region was observed between some of the mVRF cDNAs, with the number of dinucleotides varying from 7 to 11.

E24

Please replace the paragraph beginning at Page 26, line 17, with the following rewritten paragraph:

Exons 6 and 7 are contiguous in mVRF, as has been found to occur in the

E25

human homologue. The strong sequence homology between exon 6 of mVRF and hVRF (Figures 10A-10B) suggests that this sequence is not a retained intronic sequence but rather encodes a functional part of the VRF_{186} isoform.

E25 Cont

Please replace the paragraph beginning at Page 27, line 2, with the following rewritten paragraph:

Northern analysis of RNA from adult mouse tissues (muscle, heart, lung and liver) showed that expression appears to be ubiguitous and occurs primarily as a major band of approximately 1.3kb in size (Figures 14A-14E). This is somewhat different to the pattern observed for hVRF in which two major bands of 2.0 and 5.5 kb have been identified in all tissues examined. The 1.3 kb murine message presumably corresponds to the shorter of the human transcripts and the size variation thereof is most likely due to a different in the length of the respective 5' UTRs.

E26

Please replace the paragraph beginning at Page 29, line 25, with the following rewritten paragraph:

The results are shown in Figures 16A-16C. The results show that VEGF is effective in promoting neuronal survival but that this requires the presence of glial cells. Figures 17A-17C show the results of the effect of VEGF and SOM175 on three types of chick glia. The glia tested were CNS glia (Figure 17A), peripheral glia (Figure 17B) and CNS oligodendrocytes (Figure 17C). Heparin was used at 10 μg/ml in all cultures and the assay was read at 24 hours. Results were measured in ^{3}H-thymidine counts using 2000 cells per well.

E27